Artículo de investigación científica

Correlating the solubility of indomethacin in 1,4-dioxane + water mixtures by means of the Jouyban-Acree model

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Summary

In this work the validity of the Jouyban-Acree and Yalkowsky-Roseman models is evaluated to correlate the solubility of indomethacin in 1,4-dioxane + water cosolvent mixtures. The solubility correlation is studied as a function of temperature and cosolvent composition. Both models require only the experimental solubility values in the pure solvents at all the temperatures evaluated. The solubility calculated values by using both models deviate notoriously from experimental values in several cases.

Keywords: indomethacin, 1,4-dioxane + water mixtures, Jouyban-Acree and Yalkowsky-Roseman models.

Resumen

Correlación de la solubilidad de indometacina en mezclas 1,4-dioxano + agua mediante el modelo de Jouyban-Acree

En este trabajo se evaluó la utilidad de los modelos Jouyban-Acree y Yalkowsky-Roseman en la correlación de la solubilidad de la indometacina en mezclas cosolventes 1,4-dioxano + agua. La correlación de la solubilidad se estudió en función de

la temperatura y la composición cosolvente. Los dos modelos requieren únicamente los valores de solubilidad en los solventes puros a todas las temperaturas de interés. Los valores calculados se desvían significativamente de los experimentales en muchos casos.

Palabras clave: indometacina, mezclas 1,4-dioxano + agua, modelos de Jouyban-Acree y Yalkowsky-Roseman.

Introduction

Indomethacin (IMC, Fig. 1) is an anti-inflammatory drug sometimes used in actual therapeutics whose physicochemical properties have not been thoroughly studied (1, 2). In this context, it is well known that several physicochemical properties such as, the solubility and occupied volumes by active ingredients and excipients are important for all the pharmaceutical scientists, because they facilitate the processes associated to design and development of new products (3). Moreover, the reported techniques intended to predict these values are highly appreciated for practical applications because they diminish the economic and experimental efforts. These considerations imply significant reductions in costs during the design and development stages at industrial level (4).

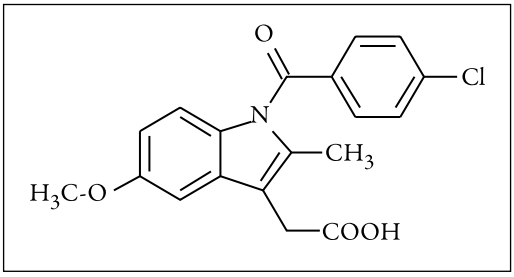

Figure 1. Molecular structure of indomethacin.

For these reasons, the main objective of this study was to evaluate the usefulness of Jouyban-Acree model (5) to correlate the equilibrium solubility of IMC in binary mixtures conformed by 1,4-dioxane and water as a function of the solvent composition and temperature. In similar way, the log-linear model proposed by Yalkowsky and Roseman (6) was also challenged in front to the experimental solubility values of this drug.

It is known that 1,2-propanediol and ethanol are the cosolvents most widely used in drug formulation design, especially those intended for peroral and parenteral administration (7, 8). Several examples of pharmaceutical formulations using these cosolvents have been presented by Rubino (7). 1,2-propanediol and ethanol are hydrogen-donor and hydrogen-acceptor solvents, and have relatively large dielectric constants, 24 and 32 at 293.15 K, respectively (9). Therefore, mixtures with low polarities could not be studied by using these two solvents when blended with water.

On the other hand, 1,4-dioxane is miscible with water in all possible compositions, although it has a low dielectric constant, 2.2 at 293.15 K (9). When this solvent is blended with water allows studying dielectric constants from 2 to 80 at room temperature. 1,4-dioxane acts just as a Lewis base in aqueous media in different way to 1,2-propanediol and ethanol that act as both Lewis donors and acceptors. Although it is a toxic solvent, it has been widely used as a model cosolvent for solubility studies of drugs by several authors (10-12).

Theoretical

The different strategies intended to estimate physicochemical properties of drugs are highly valued at industrial level. Several methods to estimate the solubility in solvent mixtures have been reported in the pharmaceutical and chemical literature (13, 14). Some of them have been challenged recently in the correlation of the equilibrium solubility of several drugs (4, 15).

The simplest model to predict drug solubility in cosolvent mixtures is the one based on the algebraic rule of mixing, which for semipolar compounds in binary mixtures takes the following form:

$$\ln X_{2-\text{Mix}} = f \ln X_{2-\text{Cosolv}} + (1-f)\ln X_{2-\text{Water}} \qquad \text{(Equation 1)}$$

where $X_{2\text{-Mix}}$ is the drug solubility calculated in the cosolvent mixture considered, $X_{2\text{-Cosolv}}$ is the drug solubility in the neat cosolvent, $X_{2\text{-Water}}$ is the drug solubility in neat water, and f is the volume fraction of cosolvent in the mixture free of drug dissolved. This last term is calculated assuming additive volumes according to:

$$f = V_{\text{Cosolv}} / (V_{\text{Cosolv}} + V_{\text{Water}}) \qquad \text{(Equation 2)}$$

where, V_{Cosolv} and V_{Water} are the respective volumes of cosolvent and water (16). Equation 1 is a practical form of the logarithmic-linear model developed by Yalkowsky and Roseman (6), which has the form:

$$\ln S_{2-\text{Mix}} = \ln S_{2-\text{Water}} + \sigma \cdot f \qquad \text{(Equation 3)}$$

where $S_{2\text{-Mix}}$ and $S_{2\text{-Water}}$ are the solubilities (as molarity or mole fraction) in the cosolvent mixture and water, respectively, and σ is the solubilizing power factor in the same solute-solvent system. The σ term in equation 3 has been correlated with several polarity indexes such as, octanol-water partition coefficients, Hildebrand solubility parameters, and interfacial tensions, among others (17).

Nevertheless, it was found experimentally that the behavior of several lipophilic solutes deviate notoriously from this simple additive rule of solubility, in particular when the solvents used are amphiprotic. As an example, in the case of propylene glycol + water mixtures, Rubino and Obeng (18) found negative deviations to equation 1 in water-rich mixtures and positive deviations in propylene glycol-rich mixtures by studying the solubility of homologous series of some alkyl *p*-hydroxibenzoates and *p*-aminobenzoates. These authors suggested that the observed deviations were due to cosolvent-water interactions, and thereby, they exposed that cosolvent interact with water by two mechanisms, namely, (i) hydrophobic hydration by forming water "icebergs" around the non-polar groups in the cosolvent, and (ii) specific interaction between the cosolvent hydroxyl group and water molecules by hydrogen bonding, which could increase the water-structure formation obtained because of the hydrophobic effect. Thus, both interactions lead to diminish the solute-solvent interactions, and therefore, the drug solubility. Opposite, in those mixtures with high cosolvent proportion the hydrogen bonding among cosolvent and water is also present but the water-structure formation has diminished or it has disappeared.

As good attempt to consider the deviations non taken into account by Equation 1 Jouyban and Acree proposed equation 4, where T is the absolute temperature and J_i are the respective polynomial coefficients. J_i coefficients have theoretical meaning because each one of them is a function of the interaction energies among two and three bodies, which in turn describe the attractions among the different molecules present in solution. Equation 4 is derivate from the equation originally proposed by Redlich and Kister (19), and its development as well as its meaning has been described previously in the literature (20, 21).

$$\ln X_{2-\text{Mix}} = f \ln X_{2-\text{Cosolv}} + (1-f)\ln X_{2-\text{Water}} + f(1-f)\sum_{i=0}^{n} \frac{J_i(f-(1-f))^i}{T} \qquad \text{(Equation 4)}$$

Recently, Jouyban and Acree (5) processed by regression analysis the reported solubility values (as mole fraction) of several drugs in 1,4-dioxane + water mixtures in front to equation 4, obtaining the equation 5, whose coefficients were statistically significant with $p < 0.05$ according to the Student's t-test.

$$\ln X_{2-\text{Mix}} = f \ln X_{2-\text{Cosolv}} + (1-f) \ln X_{2-\text{Water}} + \text{J-A factor} \qquad \text{(Equation 5)}$$

where the Jouyban-Acree factor is defined according to:

$$\text{J-A factor} = f(1-f)\left[\frac{2206.9}{T} + \frac{1173.1(f-(1-f))}{T} + \frac{1997.4(f-(1-f))^2}{T}\right]$$

The mean percentage deviation obtained by applying Equation 5 to 36 solubility data sets was 27% which is considered as good for practical purposes.

Experimental

Reagents and Materials

In this investigation the following reagents and materials were used: indomethacin accomplishing the British Pharmacopoeia quality requirements (22), 1,4-dioxane A.R. Scharlau, distilled water with conductivity < 2 μS cm^{-1}, molecular sieve Merck (numbers 3 and 4, pore size 0.3 and 0.4 nm, respectively), and Durapore® 0.45 μm filters from Millipore Corp.

Solvent mixtures preparation

All 1,4-dioxane + water solvent mixtures were prepared by mass, using an Ohaus Pioneer TM PA214 analytical balance with sensitivity ± 0.1 mg, in quantities of 50 g. The mass fractions of 1,4-dioxane of the twelve binary mixtures prepared varied by 0.10 from 0.10 to 0.70 and by 0.05 from 0.75 to 0.95.

Solubility determination

An excess of IMC was added to approximately 10 g of each solvent mixture or neat solvent, in stoppered dark glass flasks. Solid-liquid mixtures were placed with stirring in a thermostatic mechanical shaker (Julabo SW23) kept at 303.15, 308.15, or 313.15 (± 0.05) K or placed in re-circulating thermostatic baths (Neslab RTE 10 Digital One Thermo Electron Company) kept at 293.15 or 298.15 (± 0.05) K for at least 7 days to reach the equilibrium. In the case of neat water or water-rich mixtures the equilibration

time was 14 days. These equilibrium times were established by measuring the drug concentrations till they became constant. After this time the supernatant solutions were filtered (at isothermal conditions) to ensure that they were free of particulate matter before sampling. Drug concentrations were determined after appropriate dilution by measuring the light absorbance and interpolation from a previously constructed UV spectrophotometry calibration curve (UV/VIS BioMate 3 Thermo Electron Company spectrophotometer). All the solubility experiments were run in triplicate at least.

Deviation calculations

As a deviation criterion between single experimental and calculated values by means of the Yalkowsky-Roseman and Jouyban-Acree models (5), the individual percentage deviations (IPD) were calculated according to:

$$\mathrm{IPD} = 100\left(\frac{\left|X_{2-\mathrm{calc}} - X_{2-\mathrm{expt}}\right|}{X_{2-\mathrm{expt}}}\right) \qquad \text{(Equation 6)}$$

On similar way, as a general criterion of the usefulness of both equations the mean percentage deviations (MPD) were calculated by means of the equation 7, where n is the number of mixtures compositions considered.

$$\mathrm{MPD} = \frac{100}{n}\sum_{i=1}^{n}\left(\frac{\left|X_{2-\mathrm{calc}} - X_{2-\mathrm{expt}}\right|}{X_{2-\mathrm{expt}}}\right) \qquad \text{(Equation 7)}$$

Results and Discussion

It is well known that the volume expressions of mixtures concentration are dependent on temperature because the volumes of liquids change with temperature according to their thermal volume expansion coefficients (α). For this reason, Table 1 shows the temperature dependence of volume fraction in 1,4-dioxane + water mixtures with the mass composition varying in 0.10 from 0.10 to 0.70 and by 0.05 from 0.75 to 0.95 in mass fraction (μ_{Dioxane}). The respective statistical description is also showed. Although the α values for 1,4-dioxane and water are different, 1.062×10^{-3} K^{-1} and 2.51×10^{-4} K^{-1}, respectively (23), the temperature dependence of f with temperature is relatively low, being in the nine cases lower than 0.30 %, which for practical purposes is considered as almost insignificant. In all cases this variation is lower than 0.60 % and the mean values obtained at temperatures from 293.15 to 313.15 K are concordant with those

reported at 303.15 K. For this reason the volume fractions obtained at 303.15 K were used in all calculations as has been made in other similar studies (24-27).

Table 1. Volume fraction of 1,4-dioxane in 1,4-dioxane + water mixtures as a function of mixtures composition and temperature.

$\mu_{Dioxane}$	$f_{Dioxane}$						%VC [b]
	293.15 K	**298.15 K**	**303.15 K**	**308.15 K**	**313.15 K**	**Mean (SD) [a]**	
0.1000	0.0967	0.0969	0.0971	0.0973	0.0974	0.0971 (0.0003)	0.30
0.2000	0.1941	0.1944	0.1948	0.1951	0.1954	0.1948 (0.0005)	0.27
0.3000	0.2922	0.2926	0.2932	0.2936	0.2939	0.2931 (0.0007)	0.24
0.4000	0.3910	0.3916	0.3922	0.3926	0.3930	0.3921 (0.0008)	0.20
0.5000	0.4906	0.4912	0.4918	0.4923	0.4927	0.4917 (0.0008)	0.17
0.6000	0.5910	0.5915	0.5921	0.5926	0.5930	0.5920 (0.0008)	0.14
0.7000	0.6921	0.6925	0.6931	0.6935	0.6938	0.6930 (0.0007)	0.10
0.7500	0.7429	0.7433	0.7438	0.7442	0.7445	0.7437 (0.0006)	0.09
0.8000	0.7939	0.7943	0.7947	0.7950	0.7953	0.7946 (0.0005)	0.07
0.8500	0.8452	0.8454	0.8458	0.8460	0.8462	0.8457 (0.0004)	0.05
0.9000	0.8966	0.8968	0.8970	0.8972	0.8973	0.8970 (0.0003)	0.03
0.9500	0.9482	0.9483	0.9484	0.9485	0.9486	0.9484 (0.0002)	0.02

[a] SD is standard deviation. [b] %VC is percentage variation coefficient.

Table 2 shows the experimental values of equilibrium solubility for this pharmaceutical compound expressed as decimal logarithms of mole fraction. The values used as input in equations 1 and 5 were those obtained in the neat solvents at all temperatures studied.

Table 2. Experimental solubility of IMC expressed as natural logarithm as a function of mixtures composition and temperature. Values in parentheses are percentage variation coefficients in equilibrium solubility.

$\mu_{Dioxane}$	$f_{Dioxane}$	**293. K**	**298.15 K**	**303.15 K**	**308.15 K**	**313.15 K**
0.0000	0.0000	−14.063 (2.06)	−13.886 (2.43)	−13.716 (1.97)	−13.573 (1.62)	−13.396 (2.68)
0.1000	0.0971	−13.157 (1.28)	−12.974 (0.89)	−12.791 (1.11)	−12.592 (0.79)	−12.405 (0.42)
0.2000	0.1948	−12.491 (1.38)	−12.290 (0.87)	−12.058 (0.54)	−11.871 (0.25)	−11.653 (0.41)
0.3000	0.2931	−11.737 (1.63)	−11.520 (0.40)	−11.244 (1.78)	−11.061 (1.34)	−10.823 (1.26)
0.4000	0.3921	−10.317 (0.36)	−10.027 (1.40)	−9.752 (1.05)	−9.557 (0.72)	−9.239 (0.54)
0.5000	0.4917	−8.738 (1.53)	−8.469 (0.81)	−8.179 (1.13)	−7.873 (1.30)	−7.631 (0.34)
0.6000	0.5920	−7.067 (1.01)	−6.847 (1.21)	−6.451 (1.91)	−6.221 (1.46)	−5.970 (0.95)
0.7000	0.6930	−5.515 (0.22)	−5.313 (1.65)	−5.043 (1.25)	−4.790 (1.63)	−4.501 (2.12)
0.7500	0.7437	−5.038 (0.54)	−4.751 (1.01)	−4.521 (0.59)	−4.299 (0.20)	−4.095 (1.47)
0.8000	0.7946	−4.336 (1.65)	−4.141 (1.11)	−3.921 (0.74)	−3.723 (1.77)	−3.557 (2.12)
0.8500	0.8457	−3.928 (1.58)	−3.770 (0.69)	−3.608 (1.23)	−3.418 (1.50)	−3.268 (0.35)
0.9000	0.8970	−3.579 (1.53)	−3.452 (1.90)	−3.292 (1.02)	−3.163 (0.32)	−3.025 (1.31)
0.9500	0.9484	−3.326 (1.45)	−3.222 (0.77)	−3.105 (1.10)	−2.985 (1.25)	−2.873 (0.73)
1.0000	1.0000	−3.693 (0.71)	−3.540 (1.08)	−3.374 (1.62)	−3.179 (0.36)	−3.043 (0.73)

Tables 3 and 4 show the values of logarithmic solubility calculated by means of equations 1 and 5 as a function of the mixtures composition and temperature, respectively. Individual and group percentage deviations with respect to equilibrium solubilities are also showed in these tables.

Table 3. Solubility of IMC calculated by means of the Yalkowsky-Roseman additive-logarithmic model (equation 1) expressed as natural logarithm as a function of mixtures composition and temperature. Values in parentheses are individual percentage deviations calculated according to equation 6.

$f_{Dioxane}$	**293.15 K**	**298.15 K**	**303.15 K**	**308.15 K**	**313.15 K**	**MPD** [a]
0.0971	−13.057 (10.6)	−12.882 (9.6)	−12.712 (8.2)	−12.564 (2.8)	−12.391 (1.4)	7 ± 4 %
0.1948	−12.044 (56.5)	−11.871 (52.0)	−11.702 (42.8)	−11.549 (38.0)	−11.380 (31.4)	44 ± 10 %
0.2931	−11.024 (104.1)	−10.854 (94.8)	−10.685 (74.9)	−10.527 (70.6)	−10.362 (58.6)	81 ± 19 %
0.3921	−9.997 (37.6)	−9.830 (21.8)	−9.661 (9.5)	−9.498 (6.1)	−9.337 (9.3)	17 ± 13 %
0.4917	−8.964 (20.2)	−8.799 (28.1)	−8.631 (36.3)	−8.462 (44.5)	−8.305 (49.1)	36 ± 12 %
0.5920	−7.924 (57.5)	−7.761 (59.9)	−7.593 (68.1)	−7.419 (69.8)	−7.267 (72.7)	66 ± 7 %
0.6930	−6.876 (74.4)	−6.716 (75.4)	−6.549 (77.8)	−6.370 (79.4)	−6.222 (82.1)	78 ± 3 %
0.7437	−6.350 (73.1)	−6.191 (76.3)	−6.024 (77.8)	−5.842 (78.6)	−5.696 (79.8)	77 ± 3 %
0.7946	−5.822 (77.4)	−5.665 (78.2)	−5.498 (79.3)	−5.313 (79.6)	−5.169 (80.1)	79 ± 1 %
0.8457	−5.293 (74.4)	−5.136 (74.5)	−4.970 (74.4)	−4.782 (74.4)	−4.640 (74.7)	74 ± 0 %
0.8970	−4.761 (69.3)	−4.606 (68.5)	−4.439 (68.3)	−4.250 (66.2)	−4.110 (66.2)	68 ± 1 %
0.9484	−4.228 (59.4)	−4.074 (57.3)	−3.908 (55.2)	−3.715 (51.8)	−3.577 (50.6)	55 ± 4 %
						57 ± 26 [b]

[a] MPD is the mean percentage deviation at each mixture composition according to equation 7.

[b] This MPD value is the overall mean percentage deviation considering all mixture compositions.

Table 4. Solubility of IMC calculated by means of the Jouyban-Acree model (equation 5) expressed as natural logarithm as a function of mixtures composition and temperature. Values in parentheses are individual percentage deviations calculated according to equation 6.

f_{Dioxane}	293.15 K	298.15 K	303.15 K	308.15 K	313.15 K	MPD[a]
0.0971	−12.292 (137.6)	−12.130 (132.6)	−11.973 (126.6)	−11.837 (112.8)	−11.675 (107.4)	123 ± 13 %
0.1948	−10.848 (417.3)	−10.696 (392.6)	−10.546 (353.8)	−10.411 (330.4)	−10.261 (302.5)	359 ± 46 %
0.2931	−9.565 (777.7)	−9.420 (717.1)	−9.275 (616.5)	−9.139 (583.2)	−8.997 (521.2)	643 ± 103 %
0.3921	−8.333 (626.9)	−8.193 (525.4)	−8.052 (447.7)	−7.915 (416.6)	−7.779 (330.6)	469 ± 112 %
0.4917	−7.098 (415.3)	−6.965 (350.2)	−6.827 (286.6)	−6.687 (227.3)	−6.559 (192.0)	294 ± 91 %
0.5920	−5.872 (230.4)	−5.743 (201.5)	−5.609 (132.0)	−5.467 (112.5)	−5.346 (86.7)	153 ± 61 %
0.6930	−4.730 (119.1)	−4.606 (102.8)	−4.474 (76.7)	−4.328 (58.8)	−4.212 (33.5)	78 ± 34 %
0.7437	−4.235 (123.1)	−4.112 (89.6)	−3.979 (72.0)	−3.830 (59.8)	−3.716 (46.0)	78 ± 30 %
0.7946	−3.823 (67.1)	−3.699 (55.7)	−3.564 (42.9)	−3.411 (36.6)	−3.297 (29.6)	46 ± 15 %
0.8457	−3.524 (49.8)	−3.397 (45.2)	−3.260 (41.6)	−3.100 (37.5)	−2.985 (32.7)	41 ± 7 %
0.8970	−3.375 (22.7)	−3.243 (23.2)	−3.099 (21.3)	−2.931 (26.2)	−2.812 (23.7)	23 ± 2 %
0.9484	−3.416 (8.6)	−3.275 (5.2)	−3.122 (1.7)	−2.942 (4.4)	−2.817 (5.7)	5 ± 2 %
						193 ± 204 % [b]

[a] MPD is the mean percentage deviation at each mixture composition according to equation 7.

[b] This MPD value is the overall mean percentage deviation considering all mixture compositions.

By comparing the predictive results obtained for this drug by using both models it is clear that Jouban-Acree model (equation 5) is not better than additive behavior (equation 1), because of their MPD values, namely, 193 ± 204 % in the first case, in front to 57 ± 26 % in the case of equation 1. Thus, neither Yalkowsky-Roseman nor Jouyban-Acree models would be useful at industrial level if equilibrium solubility estimations within 30 or 40 % in uncertainty are allowed in the research and development of homogeneous liquid products in the pharmaceutical industry.

To see more clearly these effects, Figure 2 shows the differences obtained between experimental solubilities for IMC at 298.15 K in front to those calculated by means of equation 1. In similar way, Figure 2 also shows the differences obtained between equations 1 and 5, respectively.

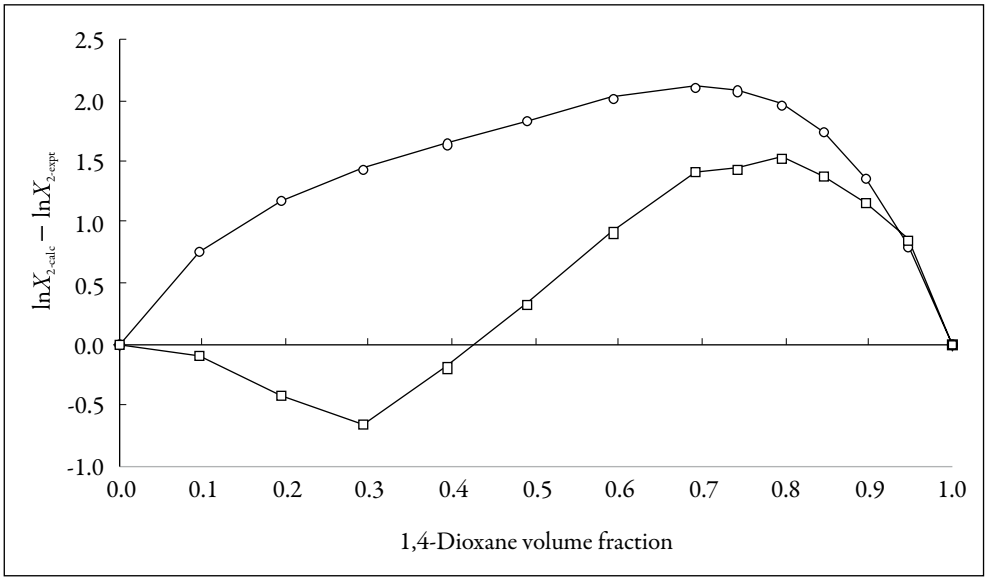

Figure 2. Logarithmic differences of IMC solubilities [(□): experimental value minus calculated value according to Yalkowsky-Roseman model (equation 1)] and logarithmic difference of calculated solubilities [(○): value according to Jouyban-Acree model (equation 5) minus value according to Yalkowsky-Roseman model (equation 1)] as a function of the 1,4-dioxane proportion in 1,4-dioxane + water mixtures at 298.15 K.

Figure 2 shows that differences obtained in front to Jouyban-Acree model are negative in all cases and dependent on solvent composition being larger in water-rich mixtures.

Thus, experimental solubilities for IMC are lower than those predicted by Equation 5. Because the equation 5 (Jouyban-Acree model) is an extension of Equation 1, Figure 2 shows the excess factor of Jouyban-Acree (J - A factor), which is equivalent to the logarithmic difference between calculated solubilities by using both equations, and it is a global excess solubility function. Besides, Figure 2 shows the logarithmic differences obtained between experimental values of IMC solubility and those calculated by assuming log-linear behavior (Equation 1). This figure also shows the differences obtained in IMC calculated solubilities by using log-linear behavior (Equation 1) and by using Equation 5 (Jouyban-Acree model) at 298.15 K.

According to Figure 2, IMC exhibits negative and positive deviations with respect to log-linear model and just negative in front to Jouyban-Acree model. It is important to note that IMC does not follow a similar trend to that described by Jouyban-Acree model which assumes positive deviations with respect to logarithmic additivity (log-linear model) in all mixtures. Thus IMC exhibits negative deviations in water-rich mixtures and positive deviations in 1,4-dioxane-rich mixtures.

The trend exhibited by IMC in Figure 2 is similar to those reported by Rubino and Obeng (18) for the solubility of homologue series of some alkyl *p*-hydroxybenzoates and *p*-aminobenzoates in propylene glycol + water cosolvent mixtures. These solutes also exhibited negative deviations in water-rich mixtures and positive in propylene glycol-rich mixtures with respect to log-linear equation.

A possible explanation for negative deviations observed in the drug solubility at low cosolvent proportions could be found in the research reported by Kimura *et al.* (28), where similar behaviors were found in dissolution enthalpies of 1-methyl-2-pyrrolidinone in ethanol + water mixtures. According to these investigators at low cosolvent proportions the water retains its ability to form ordered structures.

Although alcohols of low molar masses have been considered as polar compounds, Matsumoto *et al.* (29) based on excess molar enthalpy values have presented some evidence about the influence of the ending methyl group on the water structure formation. The interactions present between alcohols and water could diminish the interactions between water and the drug leading to lower solubility values as expected according to log-linear model.

On the other hand, at high cosolvent concentrations in the mixtures the tridimensional structure of water is lost and therefore the water molecules could be available to interact with the drug molecules. This event would lead to larger solubilities than those expected according to log-linear model (Equation 1). According to the literature another plausible explanation to positive deviations to log-linear equation could be due to

possible drug association phenomenon in the saturated solution (18). Nevertheless, in order to verify this event it would be necessary to dispose of any other kind of experimental evidence, such as organic solvent/water drug distribution coefficients at several concentrations and temperatures, or spectroscopic information.

From all topics discussed previously it follows that IMC experimental solubilities present negative deviations in front to those predicted by the Jouyban-Acree model in the 1,4-dioxane + water binary solvent system at all compositions studied. Otherwise, IMC solubility shows negative and positive deviations in front to Yalkowsky-Roseman model. These estimation differences are within 193 % as mean, whereas, Yalkowsky-Roseman model imply differences around 57 % as mean. Thus, neither Yalkowsky-Roseman nor Jouyban-Acree models would be useful at industrial level because uncertainties are greater than those usually allowed. This point remarks the great importance to determine experimentally the drug solubility in all the pharmaceutical systems as required.

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